REMARKS

I. Preliminary Remarks

Claim 1 has been amended to recite that the level of expression of AAV Rep 78 and Rep 68 proteins in the claimed cells "has not been genetically down-regulated." This amendment is supported, for example, at page 5, lines 1-6 and page 5, lines 25-27 of the specification. The Examiner objected to claim 34 for reciting "of any of claim 21." In response claim 21 is amended to delete the phrase "of any." Its inclusion was a clerical error. Claim 10 has been amended to move the phrase "supplemental AAV Rep 52 and Rep 40 proteins" in the claim to improve readability of the claim. These amendments do not include new matter.

II. The Rejections under 35 U.S.C. § 112, Second Paragraph Should be Withdrawn

Claims 1, 2, 9, 10-14 and 21-38 are rejected under 35 U.S.C. § 112, second paragraph for purportedly failing to particularly point out and distinctly claim the subject matter regarded as the invention. In particular, the Examiner asserted that the term "overexpresses AAV Rep 52 and Rep 40" in claim 1 is unclear. In addition, the Examiner maintained the rejection of claim 9 because the recitation of "derived from simian Ad SV-20" is indefinite.

The term "overexpresses AAV Rep 52 and Rep 40" in claim 1 would be understood by a person skilled in the art to mean that the cell expresses greater levels of Rep52 and Rep40 proteins than the levels obtained from the wild type native p19 promoter alone. The specification indicates that Rep 52 and Rep 40 are expressed from transcripts initiating at the p19 promoter (see page 1, lines 19-24). Moreover, each of Examples 4 through 6 describes "overexpression" of Rep 52 and Rep 40 proteins in cells in comparison to expression levels of those proteins in cell lines (*e.g.*, the D6 cell line) which express Rep 52 and Rep 40 only from the p19 promoter. That this is the comparison to be made is highlighted in Example 5 (at page 14, lines 12-14) which states "Western blot analysis revealed that the 2F10β, 2B9, and 2G2 cells lines all expressed higher levels of the rep52/40 proteins after Ad5 infection compared to standard HeLa producer cell lines (like line D6)." In the following paragraph, the 2G2 and 2F10β cells lines are specifically noted to be

"Rep52/40 overexpressing" cell lines. Claim 1 and claims dependent thereon would therefore be clear to one of ordinary skill in the art.

With respect to the term "derived from simian Ad SV-20" in claim 9, the Examiner stated that Applicants, arguments were not persuasive because it is not clear how simian Ad SV-20 of the claim related to the simian adenovirus AV-99 mentioned in Applicants' response. Applicants' reference to SV-99 in the previous response was a typographical error and should have been a reference to SV-20 instead. As was stated in the response to the previous office action, recombinant adenovirus vectors are routinely constructed by those skilled in the art by modifying the genomes of naturally occurring adenoviruses. Thus, the term "derived from" in claim 9, indicates that the recombinant adenovirus vectors were constructed starting from a simian adenovirus SV-20 genome. With the previous response, Applicant did provide an article evidencing a person skilled in the art would know what viral elements are necessary for functional recombinant adenovirus vector and would know how to make a functional recombinant adenovirus vector. Thus, in the absence of specific evidence from the Examiner refuting that article, the rejection must be withdrawn.

The Examiner also rejected claim 10 under 35 U.S.C. § 112, second paragraph asserting that it is unclear what the claimed cell comprises and what is being introduced. As noted above, Claim 10 has been amended to make the claim more readable.

In view of the foregoing amendment and remarks, the rejections under 35 U.S.C. § 112, second paragraph should be withdrawn.

III. The Rejections under 35 U.S.C. § 112, First Paragraph Should be Withdrawn

The Examiner maintained the rejection of claims 9, 14 and 19 under 35 U.S.C. § 112, first paragraph for failing to comply with the enablement requirement because the ATCC does not have an obligation to make the strain ATCC VR-199 available to the public for the required time period. However, the Examiner stated that reciting a specific strain in the claims was not necessary and suggested removal of reference to the ATCC number. The specific strain reference has therefore been deleted from the claim.

Claims 3-14, 21-29 and 31-38 were also rejected under 35 U.S.C. § 112, first paragraph because the specification assertedly does not enable methods of producing rAAV or rAAV-producing cells by "providing" AAV helper functions or introducing proteins into a cell. AAV helper functions were well known in the art at the time of filing. In addition to exemplifying multiple methods of producing rAAV, the specification references a number of illustrative documents that teach how to use helper functions to generate rAAV producing cells, such as Handbook of Parvovisuses, Vol. 1, CRC Press, Boca Raton, pp. 252-282, 1989, U.S. Patent No. 5,658,785; Clark *et al.*, Hum. Gene. Ther., 10(6):1031-1039 (1999); and Clark *et al.*, Hum. Gene. Ther., 8(6): 659-669 (1997). Copies of these documents were provided with the Information Disclosure Statement submitted on December 29, 2005. In the absence of specific evidence from the Examiner that the exemplified methods could not be repeated or that these documents fail to provide information about helper functions, this rejection must be withdrawn.

Thus, it is clear from the foregoing amendment and remarks that the pending claims are enabled by the specification. Therefore, the rejections under 35 U.S.C. § 112, first paragraph should not be maintained.

IV. The Rejections under 35 U.S.C. § 102(b) Should Be Withdrawn.

The Examiner maintained the rejection of claims 1-3, 10-13, 21, 23, 24, 30, 32 and 36 under 35 U.S.C. § 102(b) as being anticipated by Natsoulis *et al.* (U.S. Patent No. 6,027,931) or Xiao *et al.* (*J. Virol.* 72(3): 2224-2232, 1998). The Examiner indicated the rejections were maintained because the claims embrace a "wide range" of Rep78/68 expression levels because claim 1 recites the proteins are expressed at "about" the level of expression when under the control of the p5 promoter.

While Applicants dispute that either Natsoulis *et al.* or Xiao *et al.* describe host cells in which Rep 78 and Rep 68 proteins are expressed at "about" the levels of expression when under the control of the p5 promoter, Claim 1 has been amended to require that the expression of the Rep 78 and 68 proteins has not been genetically down-regulated in the recited cell. In Natsoulis *et al.*, the pRCM.globinpolyA vector (used to introduce Rep78/68 sequences to cells and relied upon by the examiner) has been genetically modified

to introduce a polyadenylation site between the transcriptional start site and the first codon in the coding sequence of the long form of Rep protein resulting in decreased expression of the long forms of Rep (Rep78 and Rep 68) in transfected cells. See column 12, lines 26-30. In Xiao *et al.*, the Rep 78 and Rep 68 were genetically down-regulated by mutation of the Rep78/68 start codon.

Claim 3 requires that an expression cassette encoding Rep 52 and Rep 40 proteins be introduced into a cell already comprising a rAAV genome, AAV rep-cap proteins and AAV helper functions. Neither Natsoulis *et al.* nor Xiao *et al.* do so. Similarly, claim 10 requires that supplemental Rep 52 and Rep 40 proteins be introduced into a cell already comprising a rAAV genome and AAV rep-cap proteins. Again, neither Natsoulis *et al.* nor Xiao *et al.* do so.

Thus, neither independent claims 1, 3 and 10 nor claims dependent thereon are expressly or inherently anticipated by Natsoulis *et al. or* Xiao *et al.* and the rejections under 35 U.S.C. § 102(b) should be withdrawn.

V. The Rejection under 35 U.S.C. § 103(a) Should Be Withdrawn

The Examiner maintained the rejection of claims 22, 26, 28 , 29 31, 35, 37 and 38 under 35 U.S.C. § 103(a) as being unpatentable over Natsoulis *et a.* (U.S. Patent No. 6,027,931) in view of Hardy (U.S. Patent No. 6,429,001). The Examiner stated that Hardy teaches that AAV host cells include the claimed cell types: HeLa, WI-38, MRC-5 and Vero. Similarly, claims 25 and 34 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Natsoulis *et al.* in view of Murphy (U.S. Patent No. 6,635,476). The Examiner stated that Murphy teaches that the PERC.6 cells line is useful for producing adenovirus and rAAV. Claims 27-29 and 36-38 were also rejected under 35 U.S.C. § 103(a) as being unpatentable over Natsoulis *et al.* in view of Potash *et al.* (U.S. Patent No. 5,911,998). The Examiner stated that Potash *et al.* teaches that the MRC-5, WI-38 and FRhL-2 cell lines may be used for vaccine production.

As the primary document, Natsoulis *et al.*, cited in the rejection does not teach or suggest methods according to the claims, combinations of it with other documents that

similarly do not teach or suggest methods as claimed do not render the claims obvious. Therefore, the rejections under 35 U.S.C. § 103(a) should be withdrawn.

CONCLUSION

In view of the foregoing amendment and remarks, Applicants believe pending claims 1-3-10, 12-14, 18, 19 and 21-38 are in condition for allowance and early notice thereof is requested. If further discussion would expedite allowance of the claims, the undersigned can be contacted at the telephone number below.

Respectfully submitted,

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